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EXAMINER	
HAGHIGHATIAN, MINA	

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1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/822,716	EDWARDS ET AL.	
	Examiner	Art Unit	
	MINA HAGHIGHATIAN	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,13-29 and 49-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10, 13-29, 49-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is a Non-Final Office Action in response to the Decision on Appeal made on 02/24/09. The following rejections are deemed necessary after further search and consideration of the claims and the Decision. Claims **1-8, 10, 13-29 and 49-52** remain pending and under examination.

Claim Rejections - 35 USC § 112

Claims 1-8, 10, 13-29 and 49-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 6-8, 10, 26-27, and 49-50 contain the indefinite terms of “less than about” and/or “more than about”. The said terms are indefinite because one of ordinary skill in the art can not determine the scope of claimed ranges. It is considered that “less than” or “more than” are set and determined limits, whereas “about” is an approximate term. It is then not clear how a set range and an approximate term can be used together. Remaining claims are rejected fro depending on a rejected base claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims **1-8, 10, 13-29 and 49-52** are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al (5,874,064) in view of Jensen et al (6,043,214).

Edwards et al teach aerodynamically light particles for drug delivery to the pulmonary system. The aerodynamically light particles are made of a biodegradable material and have a tap density less than 0.4 g/cm^3 and a mass mean diameter between 5 μm and 30 μm. The particles may be formed of biodegradable materials

such as biodegradable polymers, proteins, or other water-soluble materials. For example, the particles may be formed of a functionalized polyester graft copolymer consisting of a linear α-hydroxy-acid polyester backbone having at least one amino acid residue incorporated per molecule therein and at least one poly(amino acid) side chain extending from an amino acid group in the polyester backbone. Other examples include particles formed of water soluble excipients, such as trehalose or lactose, or proteins, such as lysozyme or insulin. The aerodynamically light particles can be used for enhanced delivery of a therapeutic agent to the airways or the alveolar region of the lung. The particles incorporating a therapeutic agent may be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of a wide variety of therapeutic agents (see Abstract, Summary and col. 4). The amino acid is selected from the group consisting of aspartic acid, lysine and alanine (see claim 7). The said aerodynamically light particles also have an aerodynamic diameter of from 1 and 3 μm (see claims 1 and 16). The aerodynamically light particles incorporate a therapeutically active agent such as peptides and proteins including **insulin** (see col. 10, lines 1-10 and 40-45). The particles are prepared by spray-drying (see Example 3).

Edwards et al, lacks disclosure on multivalent metal cation. This deficiency is cured by Jensen et al (6,043,214).

Jensen et al teaches preparation of a therapeutic powder formulation comprising particles composed of insulin or an analogue thereof and an enhancer. In a preferred embodiment Jensen et al teach that the formulations also comprise zinc preferably in an

amount corresponding to 2 Zn atoms/insulin hexamer to 12 Zn atoms/insulin hexamer (see col. 3, lines 41-47). In Example 1, 625.9 mg of insulin was dissolved in water by adding 2N HCL resulting in a pH of 3.6-3.7 and 1.25 µL of 4% zinc chloride solution was added and mixed. The enhancer is advantageously a surfactant selected from the group consisting of salts of fatty acid, bile salts or phospholipids. Lysophosphatidylcholine is preferred phospholipid (see col. 3, lines 1-6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made given the teachings of Edwards et al to have looked in the art for other varieties of active agents for ultimate benefit from the treatment such as insulin zinc as taught by Jensen et al with reasonable expectation of successful administration of light particles to the patients pulmonary system. In other words, **all the claimed elements** were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Edwards et al teach aerodynamically light particles comprising an active agent to the pulmonary system. Jensen et al teach combination of insulin and zinc for sustained release of insulin to the pulmonary system.

Claims **1-8, 10, 13-17, 21, 24-28 and 49-51** are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al (5,985,309) in view of Christensen (3,102,077).

Edwards et al teach particles incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for drug delivery to the pulmonary system, and methods for their synthesis and administration. In a preferred embodiment, the particles are made of a biodegradable material and have a tap density less than 0.4 g/cm^3 and a mass mean diameter between 5 μm and 30 μm, which together yield an aerodynamic diameter of the particles of between approximately one and three microns. The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of poly(lactic acid) or poly(glycolic acid) or copolymers thereof. Alternatively, the particles may be formed solely of a therapeutic or diagnostic agent and a surfactant. Exemplary surfactants include phosphoglycerides such as dipalmitoyl phosphatidylcholine (DPPC). The particles can be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of a wide variety of therapeutic agents. Formation of complexes of positively or negatively charged therapeutic agents with molecules of opposite charge can allow control of the release rate of the agents into the blood stream following administration (see abstract and summary). Suitable therapeutic agents include proteins and peptide such as **insulin**. Those therapeutic agents which are charged, such as most of the proteins, including insulin, can be administered as a complex between the charged

therapeutic agent and a molecule of opposite charge. Preferably, the molecule of opposite charge is a charged lipid or an oppositely charged protein (see col. 12, lines 1-47). In Figure 5, insulin plasma levels of 4 different formulations are shown. In both subcutaneous and inhalation delivery, the formulations that contained insulin and zinc had higher plasma levels. Edwards '309 does not specifically disclose the multivalent metal cation (the charged molecule). However this deficiency is cured by Christensen.

Christensen teach preparation of insulin containing 2.75 to 8% zinc. Christensen disclosed that zinc-insulin amorphous or crystalline form with chemically bound zinc content of as high as 6% and even as high as 8% (see col. 2, lines 26-31). In Example 13, Christensen discloses preparation of an amorphous insulin with zinc content of about 4.5%. In Example 15, the resulting crystals contained 5% zinc. It is also disclosed that in all of the said examples, amorphous insulin may be used instead of crystalline insulin.

Edwards et al does not anticipate the powder formulations for pulmonary delivery of an active agent, comprising insulin and zinc, however it teaches advantages of combining proteins such as insulin with charged molecules. Christensen discloses the combination of a zinc salt with insulin and the advantages of doing such. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared the powder formulations as taught by Edwards et al and Christensen because it is disclosed that such combination provides for sustained release of the

charged active agent. The combination of the two teachings would have lead one of ordinary skill in the art to the claimed invention. In other words, **all the claimed elements** were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claims **1-8, 10, 13-19, 21-29 and 49-52** are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al (6,136,295) in view of Jensen et al (6,043,214).

Edwards et al teach aerodynamically light particles for drug delivery to the pulmonary system, and methods for their synthesis and administration are provided. In a preferred embodiment, the aerodynamically light particles are made of a biodegradable material and have a tap density less than 0.4 g/cm^3 and a mass mean diameter between 5 μm and 30 μm. The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of a functionalized polyester graft copolymer consisting of a linear α-hydroxy-acid polyester backbone having at least one amino acid group incorporated therein and at least one poly(amino acid) side chain extending from an amino acid group in the polyester backbone. In one embodiment, aerodynamically light particles having a large mean diameter, for example greater than 5 μm can be used for enhanced delivery of a therapeutic agent to the alveolar region of the lung. The aerodynamically light particles

incorporating a therapeutic agent may be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of wide variety of therapeutic agents (see Abstract and Summary).

Edwards et al also teach that in a preferred embodiment, comb-like graft copolymers are used which include a linear polyester backbone having amino acids incorporated therein, and poly(amino acid) side chains which extend from the amino acid residues in the polyester backbone. The polyesters may be polymers of .alpha.-hydroxy acids such as lactic acid, glycolic acid, hydroxybutyric acid and hydroxy valeric acid, or derivatives or combinations thereof. The inclusion of ionizable side chains, such as polylysine, in the polymer has been found to enable the formation of more aerodynamically light particles, using techniques for making microparticles known in the art, such as solvent evaporation. Other ionizable groups, such as amino or carboxyl groups, may be incorporated, covalently or noncovalently, into the polymer to enhance surface roughness and porosity. For example, polyalanine could be incorporated into the polymer (col. 7, lines 25-37). Suitable therapeutic agents include polypeptides and proteins such as **insulin** (see col. 10, lines 1-45). Edwards et al lack specific disclosure on multivalent metal cation such as zinc. This deficiency is cured by Jensen et al.

Jensen et al teaches preparation of a therapeutic powder formulation comprising particles composed of insulin or an analogue thereof and an enhancer. In a preferred embodiment Jensen et al teach that the formulations also comprise zinc preferably in an amount corresponding to 2 Zn atoms/insulin hexamer to 12 Zn atoms/insulin hexamer

(see col. 3, lines 41-47). In Example 1, 625.9 mg of insulin was dissolved in water by adding 2N HCL resulting in a pH of 3.6-3.7 and 1.25 µL of 4% zinc chloride solution was added and mixed. The enhancer is advantageously a surfactant selected from the group consisting of salts of fatty acid, bile salts or phospholipids. Lysophosphatidylcholine is preferred phospholipid (see col. 3, lines 1-6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made given the teachings of Edwards et al to have looked in the art for other varieties of active agents for ultimate benefit from the treatment such as insulin zinc as taught by Jensen et al with reasonable expectation of successful administration of light particles to the patient's pulmonary system. In other words, **all the claimed elements** were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Edwards et al teach aerodynamically light particles comprising an active agent to the pulmonary system. Jensen et al teach combination of insulin and zinc for sustained release of insulin to the pulmonary system.

Claims **1-8, 10, 13-29 and 49-52** are rejected under 35 U.S.C. 103(a) as being unpatentable over Vanbever et al (7,052,678) as evidenced by Christensen (3,102,077).

Vanbever et al teach a method for pulmonary delivery of therapeutic, prophylactic and diagnostic agents to a patient wherein the agent is released in a sustained fashion, and to particles suitable for use in the method. In particular, the invention relates to a method for the pulmonary delivery of a therapeutic, prophylactic or diagnostic agent comprising administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of particles comprising a polycationic complexing agent which is complexed with a therapeutic, prophylactic or diagnostic agent or any combination thereof having a charge capable of complexing with the polycationic complexing agent upon association with the bioactive agent. The particles can further comprise a pharmaceutically acceptable carrier. The amount of polycationic complexing agent present in the particles is an amount sufficient to sustain the release of diagnostic, therapeutic or prophylactic agent from the particles. For example, the amount of complexing agent present can be at about 5% weight/weight (w/w) or more of the total weight of the complexing agent and therapeutic, diagnostic or prophylactic agent. Release of the agent from the administered particles occurs in a sustained fashion (see abstract and summary). The particles, can further comprise a carboxylic acid which is distinct from the bioactive agent and polycationic complexing agent. In one embodiment, the carboxylic acid includes at least two carboxyl groups. Carboxylic acids include the salts thereof as well as combinations of two or more carboxylic acids and/or salts thereof. In a preferred embodiment, the carboxylic acid is a hydrophilic carboxylic acid or salt thereof. Citric acid and citrates, such as, for example sodium citrate, are

preferred. Combinations or mixtures of carboxylic acids and/or their salts also can be employed (paragraph bridging col. 2 and col. 3).

Vanbever et al also disclose that the particles suitable for use in the invention can further comprise an amino acid which is distinct from the polycationic complexing agent. In a preferred embodiment the amino acid is hydrophobic. In a particular embodiment, the particles can be in the form of a dry powder suitable for inhalation. The particles can have a tap density of less than about 0.4 g/cm^3, preferably less than about 0.1 g/cm^3. Further, the particles suitable for use in the invention can have a median geometric diameter of from about 5 micrometers to about 30 micrometers. In yet another embodiment, the particles suitable for use in the invention have an aerodynamic diameter of from about 1 to about 5 microns (col. 3, lines 4-16).

It is disclosed that, the invention has numerous advantages. For example, particles suitable for inhalation can be designed to possess a sustained release profile. This sustained released profile provides for prolonged residence of the administered bioactive agent in the lung and thereby, increases the amount of time in which therapeutic levels of the agent are present in the local environment or systemic circulation. The sustained release of agent provides a desirable alternative to injection therapy currently used for many therapeutic, diagnostic and prophylactic agents requiring sustained release of agent, such as insulin for the treatment of diabetes. In addition, the invention provides a method of delivery to the pulmonary system wherein the high initial release or burst of agent typically seen in inhalation therapy is reduced. Consequently, patient compliance and comfort can be increased by not only reducing

frequency of dosing, but by providing a therapy which is more amenable and efficacious to patients (col. 3, lines 17-33).

Vanbever et al teach that most preferably, the polycationic agent, protamine is complexed with insulin (col. 5, lines 45-47). The complexing agent is present in an amount of from 5% to about 35% w/w of the total weight of the formulation (see col. 6, lines 30-45). The said particles can further comprise a multivalent metal cation such as zinc, calcium, etc (see col. 6, lines 58-67). The metal cation can be complexed with the bioactive agent using the conditions described above for complexation with the polycationic complexing agent. The amount of multivalent metal cation includes both multivalent metal cation which is complexed with the biologically active agent, as well as any multivalent metal cation which is present but not complexed with the biologically active agent. The particles of the invention can, when desired, further comprise a pharmaceutically acceptable carrier. Suitable pharmaceutically acceptable carriers can be chosen, for example, based on achieving particles having the desired characteristics for inhalation to the area of the respiratory tract where delivery is needed and therapeutic action is achieved. Pharmaceutically acceptable carriers suitable for use in the invention include, phospholipids, sugars and polysaccharides, such as maltodextrin (see col. 7, lines 1-23).

Preferably, the pharmaceutically acceptable carrier of the particles is a phospholipid. Examples of suitable phospholipids include, among others, phosphatidic acids, phosphatidylcholines, phosphatidylalkanolamines such as a phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines,

phosphatidylinositols and combinations thereof. Specific examples of phospholipids include, 1,2-diacyl-sn-glycero-3-phosphocholine and a 1,2-diacyl-sn-glycero-3-phosphoalkanolamine phospholipids. Suitable examples of 1,2-diacyl-sn-glycero-3-phosphocholine phospholipids include, but are not limited to, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dilaureoyl-sn-3-glycero-phosphocholine (DLPC), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) (see col. 7, lines 24-65).

Vanbever et al teach that the particles suitable for use in the invention can further comprise an amino acid. In a preferred embodiment the amino acid is hydrophobic. Suitable naturally occurring hydrophobic amino acids, include but are not limited to, leucine, isoleucine, alanine, valine, phenylalanine, glycine and tryptophan. Combinations of hydrophobic amino acids can also be employed (col. 9, lines 54-60).

Vanbever et al additionally teach that a solution of aqueous human zinc insulin was prepared, the pH was adjusted and added to a protamine containing solution. The formulation was then dried to prepare powders (see col. 21, line 53 to col. 22, line 6).

While Vanbever et al is clearly disclosing adding a multivalent metal zinc to the powder formulation of insulin, the amount of zinc is not clearly disclosed. This deficiency is cured by Christensen.

Christensen teach preparation of insulin containing 2.75 to 8% zinc. Christensen disclosed that zinc-insulin amorphous or crystalline form with chemically bound zinc

content of as high as 6% and even as high as 8% (see col. 2, lines 26-31). In Example 13, Christensen discloses preparation of an amorphous insulin with zinc content of about 4.5%. In Example 15, the resulting crystals contained 5% zinc. It is also disclosed that in all of the said examples, amorphous insulin may be used instead of crystalline insulin.

Edwards et al does not anticipate the powder formulations for pulmonary delivery of an active agent, comprising insulin and zinc, wherein the amount of zinc is more than 1%, however it teaches advantages of combining proteins such as insulin with multivalent metal cations such as zinc. Christensen discloses the combination of a zinc salt with insulin and the advantages of doing such. The amount of zinc in the formulation is as high as 8%. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared the powder formulations as taught by Edwards et al and Christensen because it is disclosed that such combination provides for sustained release of the charged active agent. The combination of the two teachings would have lead one of ordinary skill in the art to the claimed invention. In other words, **all the claimed elements** were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claims **1-8, 10, 13-17, 21, 24-28 and 49-51** are rejected under 35 U.S.C. 103(a) as being unpatentable over Platz et al (7,097,827) in view of Jensen et al (6,043,214).

Platz et al teach dispersible dry powder pharmaceutical-based compositions. The said dispersible dry powder pharmaceutical-based composition is one having a moisture content of less than about 3% by weight (% w) water; a particle size of about 1.0-5.0 μm mass median diameter (MMD), and preferably 1.0-3.0 μm MMD; a delivered dose of about >30%, and most preferred >60%; and an aerosol particle size distribution of about 1.0-5.0 μm mass median aerodynamic diameter (MMAD), usually 1.5-4.5 μm MMAD, and preferably 1.5-4.0 MMAD (see Abstract and Summary). Suitable active agents include polypeptides and proteins such as insulin (col. 6, lines 3-10) and suitable excipients include polysaccharides and amino acids. Suitable amino acids include alanine and glycine. Suitable pH adjusters include organic acids (see col. 6, line 50 to col. 7, line 14). The powders are made by spray drying the solution (col. 8, lines 44-67).

Platz et al also disclose a 20% insulin formulation for pulmonary delivery which includes zinc citric acid and is spray dried to powders. In claims 1-5, it is disclosed that the particles have a tap density of less than 0.4 g/cm^3, a particle size of less than 10 μm and an MMAD of about 1 μm. Platz et al does not specifically recite the amount of zinc in the insulin and does not recite use of phospholipids. The said deficiencies are cured by Jensen et al.

Jensen et al teaches preparation of a therapeutic powder formulation comprising particles composed of insulin or an analogue thereof and an enhancer. In a preferred embodiment Jensen et al teach that the formulations also comprise zinc preferably in an amount corresponding to 2 Zn atoms/insulin hexamer to 12 Zn atoms/insulin hexamer (see col. 3, lines 41-47). In Example 1, 625.9 mg of insulin was dissolved in water by adding 2N HCL resulting in a pH of 3.6-3.7 and 1.25 µL of 4% zinc chloride solution was added and mixed. The enhancer is advantageously a surfactant selected from the group consisting of salts of fatty acid, bile salts or phospholipids. Lysophosphatidylcholine is preferred phospholipid (see col. 3, lines 1-6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made given the powder formulations of Platz et al comprising insulin, zinc and citric acid and its teachings of amino acids as suitable excipients, to have looked in the art for the amounts of zinc and for other suitable excipients for the powder formulations of insulin as taught by Jensen et al with reasonable expectation of successfully delivering an active agent to the pulmonary system through spray dried powder formulations. In other words, **all the claimed elements** were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claims **1-8, 10, 13-17, 26-27 and 49-50** are rejected under 35 U.S.C. 103(a) as being unpatentable over Maa et al (6,284,282) in view of Christensen (3,102,077).

Maa et al discloses a method of spray freeze drying proteins for pharmaceutical administration. The said dry powder compositions comprising particles of a protein of a mean diameter of less than 5 micron (col. 2, lines 10-20). In a preferred embodiment, the spray freeze dried powders are characterized on the basis of their average particle size. Preferably the average particle size ranges from 5 to 30 micron (col. 5, lines 48-53). The protein particles are also said to have a tap density of less than about 0.8 g/cm^3, with a tap density of less than about 0.4 g/cm^3 being preferred and less than about 0.1 g/cm^3 being especially preferred (col. 6, lines 5-12). Maa et al discloses proteins which include **insulin** (col. 6, line 46). The compositions of the invention may also comprise preservatives, detergents, surfactants, antioxidants etc (see col. 11, lines 15-17). Maa lacks specific disclosure on addition of a multivalent metal cation. This deficiency is cured by Christensen.

Christensen teach preparation of insulin containing 2.75 to 8% zinc. Christensen disclosed that zinc-insulin amorphous or crystalline form with chemically bound zinc content of as high as 6% and even as high as 8% (see col. 2, lines 26-31). In Example 13, Christensen discloses preparation of an amorphous insulin with zinc content of about 4.5%. In Example 15, the resulting crystals contained 5% zinc. It is also disclosed that in all of the said examples, amorphous insulin may be used instead of crystalline insulin.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Maa et al on spray dried powder formulations containing proteins and peptides such as insulin, with tap density of less than 0.1 and particle size of from 5 to 30 microns with the teachings of Christensen on insulin powders with high content of zinc, With a reasonable expectation of successful delivery of a sustained release insulin formulation to the patient's pulmonary system for better control of disorders such as diabetes. In other words, the claims would have been obvious because the technique for improving a particular formulation was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **1-8, 10, 13-17, 21, 24-28 and 49-51** are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 5,985,309 in view of Christensen (3,102,077). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. The claims of the US Patent '309 are drawn to particles and a method for drug delivery to the pulmonary system comprising a therapeutic agent and a molecule having a charge opposite to the charge of the therapeutic agent and forming a complex thereto and wherein the particles have a tap density of less than 0.4 g/cm^3,a geometric diameter of from about 5 to about 30 microns and an aerodynamic diameter of from about 1 to about 5 microns. The depending claims are drawn to addition of additives such as phospholipids, fatty acids and polymers. Insulin is also one of the preferred active agents. The claims of the instant application are drawn to the same method with the same limitations. The difference is that in the US Patent '309 the specific multivalent cation is not identified, while in the instant application the multivalent cation is a identified as zinc. Christensen et al teaches that zinc insulin complexes are known and beneficial for sustained release therapy. Thus one of ordinary skill in the art would have been motivated to have looked in the art for specific multivalent metal cation suitable for combination with insulin, as taught by Christensen et al with reasonable expectation of success. In other words, the claims would have been obvious because a person of

ordinary skill has good reasons to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Claims 1-8, 10, 13-17, 24-28 and 49-51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 8-48 of U.S. Patent No. 7,052,678 in view of Jensen et al (6,043,214). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. The claims of the US Patent '678 are drawn to a method of delivery to the pulmonary system comprising administering to the respiratory tract of a patient an effective amount of a dry powder having a tap density of less than 0.1 g/cm^3 and comprising a polycationic complexing agent, complexed with the therapeutically active agent. The depending claims are drawn to particulate formulations having a geometric diameter of from about 5 to about 30 microns and an aerodynamic diameter of from about 1 to about 5 microns, and other additives such as phospholipids, amino acids and organic acids. The claims of the instant application are drawn to the same method with the same limitations. The difference is that in the US Patent '678 the complexing agent is a polycationic complexing agent while in the instant application the complexing agent is a multivalent metal cation. Jensen et al teaches that zinc insulin complexes are known and beneficial for sustained release therapy. Thus one of ordinary skill in the art would have been motivated to have substituted one complexing agent for another with reasonable

expectation of success. In other words, the claims would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claims **1-8, 10, 13-17, 21, 24-28 and 49-51** are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,652,837 in view of Jensen et al (6,043,214). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. The claims of the US Patent '837 are drawn to particles for and a method for delivery to the pulmonary system comprising administering to the respiratory tract of a patient an effective amount of a dry powder having a tap density of less than 0.4 g/cm^3 and comprising an active agent and a molecule having a charge opposite to the charge of the active agent. The particulate formulation having a geometric diameter of from about 5 to about 30 microns and an aerodynamic diameter of from about 1 to about 5 microns, and other additives such as phospholipids, polymers and fatty acids. The claims of the instant application are drawn to the same method with the same limitations. The difference is that in the US Patent '837 the nature of the charged molecule is not identified, while in the instant application the active agent is complexed with a multivalent metal cation. Jensen et al teaches that zinc insulin complexes are known and beneficial for sustained release therapy. Thus one of ordinary skill in the art would have been motivated to have looked in the art for specific charged molecules suitable or

complexation with active agents such as insulin. Jensen teach that zinc complexed with insulin is known. In other words, the claims would have been obvious because a person of ordinary skill has good reasons to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Claims 1-8, 10, 13-17, 24-28 and 49-51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-50 of U.S. Patent No. 6,749,835 in view of Jensen et al (6,043,214). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. The claims of the US Patent '835 are drawn to a method of delivery to the pulmonary system comprising administering to the respiratory tract of a patient an effective amount of a dry powder having a tap density of less than 0.4 g/cm^3 and an aerodynamic diameter of from about 1 to about 5 microns, comprising an active agent, a hydroxydicarboxylic acid, a phospholipid and a multivalent cation or anion. The depending claims are drawn to particulate formulations having a geometric diameter of from about 5 to about 30 microns. The claims of the instant application are drawn to the same method with the same limitations. The difference is that in the US Patent '835, depending claims are drawn to albuterol as the active agent and calcium as the multivalent metal cation. In the instant application the multivalent metal cation of choice is zinc and the active agent of choice is a protein or peptide such as insulin. Jensen et al teaches that zinc insulin

complexes are known and beneficial for sustained release therapy. Thus one of ordinary skill in the art would have been motivated to have substituted one multivalent cation for another and one active agent for another as taught by Jensen et al with reasonable expectation of success. In other words, the claims would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claims 1-8, 10, 13-17, 24-28 and 49-51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-47 of U.S. Patent No. 7,048,908 in view of Jensen et al (6,043,214). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious over the reference claims. The claims of the US Patent '908 are drawn to a method of delivery to the pulmonary system comprising administering to the respiratory tract of a patient a bioactive agent in association with a charged lipid wherein the charged lipid has an overall net positive charge and the agent has an overall net negative charge. The depending claims are drawn to the active agent being insulin, the tap density of particles being less than 0.4 g/cm^3, the aerodynamic diameter being from about 1 to about 5 microns, geometric diameter of from about 5 to about 30 microns and the particles further comprising a multivalent salt of a metal. The claims of the instant application are drawn to the same method with the same limitations. The difference is that in the US Patent '908, the multivalent metal cation is not identified. In the instant application the multivalent metal

cation of choice is zinc. Jensen et al teaches that zinc insulin complexes are known and beneficial for sustained release therapy. Thus one of ordinary skill in the art would have been motivated to have looked in the art for specific multivalent metal cations suitable for combination with insulin, as taught by Jensen et al with reasonable expectation of success. In other words, the claims would have been obvious because a person of ordinary skill has good reasons to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Claims 1-2, 4, 8, 10, 13-17, 24-28 and 49-51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 7,279,182. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been anticipated by the reference claims. The claims of the US Patent '182 are drawn to a method of preparing particles having a tap density of less than 0.4 g/cm^3 comprising forming a mixture including a therapeutically active agent, a hydroxydicarboxylic acid, a phospholipid a solvent and a multivalent cation or anion and wherein the particles are spray dried. The depending claims are drawn to the aerodynamic diameter being from about 1 to about 5 microns, geometric diameter of from about 5 to about 30 microns. The claims of the instant application are drawn to a method of delivery to the pulmonary system the particles made as in '182. the remaining limitations are the same or similar.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINA HAGHIGHATIAN whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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